Delayed lichenoid drug eruption associated with apremilast

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INTRODUCTION

Apremilast is a phosphodiesterase-4 inhibitor approved by the Federal Drug Association for treatment of psoriatic arthritis, moderate to severe plaque psoriasis, and Behcet's disease. Benefits of this medication include oral administration, lack of requirement for routine laboratory monitoring, a relatively safe adverse effect profile, and powerful immunomodulatory effects without strong immunosuppressive activity.[1]

Reports of cutaneous toxicity associated with the use of apremilast are rare. To our knowledge, there has been only 1 other reported case of lichenoid drug eruption (LDE) attributed to apremilast.[2] Herein, we present a delayed LDE occurring approximately 3.5 years after initiation of apremilast for psoriasis.

CASE PRESENTATION

A 46-year-old Asian male presented to our clinic with classic plaque psoriasis. His body surface area was 20%. The patient was taking an angiotensin converting enzyme inhibitor, lisinopril, for treatment of hypertension.

Topical steroids and hypoallergenic products were initiated. The patient improved greatly but noted that his psoriatic plaques returned quickly when the topical therapy schedule was not followed. After discussion regarding systemic treatment options, therapy with apremilast was initiated. The patient tolerated the apremilast well and achieved good control of his psoriasis.

Approximately 3 years after initiation of apremilast, the patient noted progressively increasing pruritus involving his lower extremities. On exam, a few lesions consistent with prurigo nodularis were noted (Fig 1). His body surface area at this time was 3%. Tapinarof cream was added to his treatment regimen, and he improved.

Abbreviations used:

ACE: angiotensin converting enzyme
BSA: body surface area
LDE: lichenoid drug eruption
PN: prurigo nodularis

Six months later, the patient called reporting 10 of 10 itching on his legs, and he perceived that his psoriasis was worsening. A phone visit was initiated, and he described open sores on his bilateral legs. Doxycycline was prescribed, and tapinarof was discontinued to exclude the possibility of an allergic contact reaction.

Two weeks later, the patient reported continued severe pruritus. On exam, body surface area was 3%. In addition, nonconfluent plaques with a violaceous hue were noted on the lower legs; Wickham striae were not observed (Fig 2). No mucosal lesions were present. The patient was prescribed hydroxyzine and a prednisone taper. Two skin biopsies were performed.

Risankizumab therapy was initiated while weaning off apremilast. The patient's pruritus remained until 24 hours after the last dose of apremilast, at which time his pruritus immediately decreased to 1 of 10.

Skin biopsy was obtained from the left thigh. Histopathologic features included compact

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Fig 1. Three years after initiation of apremilast, prurigo nodularis lesions were noted.

Fig 2. Nonconfluent plaques with a violaceous hue were noted on the lower legs; Wickham striae were not observed. A 6 month time period has elapsed from the noted prurigo nodularis lesions.

orthokeratosis with foci of parakeratosis, mild hypergranulosis, and irregular epidermal acanthosis. Interface dermatitis was present, associated with dyskeratotic cells along and scattered above the basal zone. A perivascular and interstitial inflammatory infiltrate composed of lymphocytes and histiocytes was observed, and melanophages were present (Fig 3). The histopathologic differential included a lichenoid drug reaction versus lichen planus versus a viral exanthem versus connective tissue disease.

The patient was offered a rechallenge of apremilast, both orally and in a patch test form, to ensure this was the definitive culprit of his rash and severe pruritus. He politely declined. Follow-up examination revealed macular areas of postinflammatory hyperpigmentation in areas where the lichenoid lesions were previously located; no new lesions were noted.

DISCUSSION

Our patient developed a lichenoid drug eruption approximately 3.5 years after initiation of apremilast. Although most drug eruptions occur 1-2 weeks after initiation of the inciting medication, the latent period has been shown to be longer for LDE, ranging from 2 months to 3 years in some cases.[3] A latent period from 3 to 6 months has been reported for angiotensin converting enzyme inhibitors.[3]

The clinical presentation of LDE can be similar to idiopathic lichen planus, but several clinical features may help distinguish the entities from 1 another.[3] Distribution of the eruption over the trunk and limbs, photo distribution, presence of scale, absence of Wickham striae, absent oral involvement, and increased postinflammatory hyperpigmentation after resolution of the eruption are features that favor LDE over idiopathic lichen planus.

Maloney et al summarized extremely rare reported adverse effects of apremilast, including chronic tearing, lichenoid reaction, peripheral neuropathy, hyperpigmentation, Fanconi syndrome, purpura annularis telangiectodes of Majocchi, and appearance of lentigines on resolving psoriatic plaques.[4]

Skin toxicity due to apremilast is rare.[5] In addition to the above-mentioned rare cases, a case report of apremilast-associated drug reaction with eosinophilia and systemic symptoms in a patient treated for pityriasis rubra pilaris occurred 6 weeks after initiation of therapy.[5]

One other cutaneous lichenoid eruption from apremilast was found in the literature.[2] This was confirmed by histopathologic analysis after 60 days of taking apremilast for discoid lupus erythematosus. The eruption regressed 3 weeks after discontinuing apremilast.

There are several histopathologic features observed in this case that favor the diagnosis of a lichenoid drug reaction over lichen planus.[6] The stratum corneum contained foci of parakeratosis, scattered dyskeratotic cells were present above the basal zone, and the density of melanophages within the papillary dermis was greater than what is typically seen in lichen planus. In addition, the lichenoid infiltrate in typical cases of lichen planus tends to be more dense and interface-obscuring than the infiltrate observed in this case. Eosinophils are commonly present in drug reactions but were not observed in the inflammatory infiltrate in this case. However, the absence of eosinophils does not exclude a drug reaction. The current case serves as a valuable reminder to include a drug reaction in the differential of interface dermatitis without eosinophils, in the appropriate clinical context.

Other considerations in the histopathologic differential included a viral exanthem or postviral dermatosis versus connective tissue disease. These entities

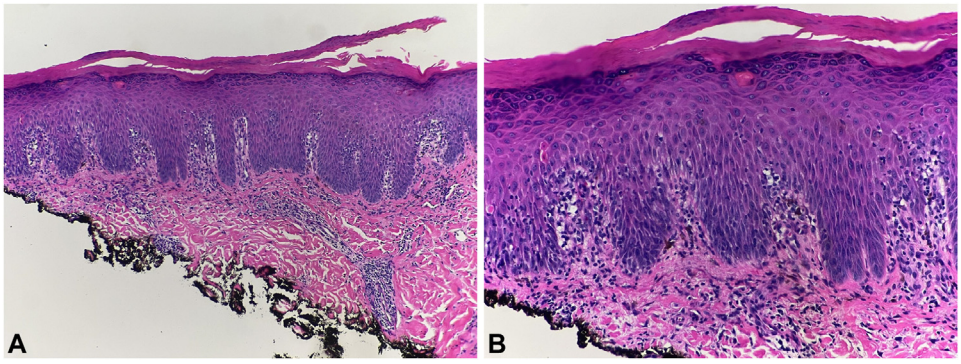

Fig 3. Lichenoid interface dermatitis with features favoring lichenoid drug eruption. **A,** Compact orthokeratosis with foci of parakeratosis, mild hypergranulosis, and irregular epidermal hyperplasia (original magnification ×100). **B,** Interface dermatitis with patchy lichenoid inflammation, scattered suprabasal dyskeratotic cells, and melanophages in papillary dermis (original magnification ×200).

could not be excluded based on histopathologic features alone, so correlation with the clinical presentation and response to treatments or interventions is essential. In this case, the rapid resolution of the patient's pruritus following discontinuation of apremilast strongly favors a drug-induced etiology.

The delayed LDE described in this report represents a rare cutaneous adverse effect associated with apremilast. The unusually long latent period for this reaction serves as a reminder that a drug reaction should not be excluded from the clinical differential in patients who have been on a medication for several years.

DESCRIPTION

This case report describes a delayed lichenoid eruption to apremilast 3.5 years after initiation. Cutaneous toxicity associated with use of apremilast is rare. Because I didn't suspect apremilast, this patient remained on this medication for about 2 months. Side effects of these medications, no matter how rare, should be reported to ensure the highest level of care for our patients.

Conflicts of interest

None disclosed.

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